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General introduction and outline of the thesis

‘Some 2.4 billion years ago, photosynthesis lead to the accumulation of oxygen to levels that were likely toxic to many obligate anaerobes. Organisms that could defend themselves against oxidative stress, and at the same time utilize oxygen for energy, survived and evolved. As time went on, a cellular requirement for oxygen became critical, and animals developed a biochemical response to low levels of oxygen.’

Sally L. Dunwoodie, The Role of Hypoxia in Development of the Mammalian Embryo[1]

General introduction

The fetal circulation

Fetal cardiac development starts in the third week of gestation.[2] Innervation of the heart occurs at five weeks and by eight weeks it has developed into a four-chambered system resembling the adult heart.[2] Throughout gestation the heart continues to grow and adapt to increasing hemodynamic demands.[3] Lung development starts at four weeks gestational age.[4] The formation of sacculi from the terminal bronchioles with a first primitive air-blood-barrier, however, only begins at about 24 weeks gestational age, which limits effective ventilation of those born earlier.[4] By 32 weeks, septation of the terminal sacs begins along with maturation of the surfactant system and capillary network and by 36 weeks the first true thin-walled alveoli responsible for effective gas exchange are visible.[4]

Until birth, the fetal lungs are filled with amniotic fluid and the fetus depends on oxygen and nutrient supply via the placenta. Therefore, the fetal circulation has to be different from the postnatal circulation. In short, highly oxygenated blood from the placenta is transported through the umbilical vein towards the liver. Half of the oxygenated blood is shunted away from the liver towards the heart through the ductus venosus.[2,5] Although it mixes with de-oxygenated blood returning from fetal body parts into the vena cava, most of the oxygenated blood is directed towards the left atrium.[2,5] From here, it follows the pressure gradient into the right atrium through a second shunt, the foramen ovale.[2,5] Bypassing the right ventricle and lungs, well-oxygenated blood is thus directly shunted towards the left ventricle, which supplies the brain, heart, and upper limbs.[2,5] Before descending further towards the lower fetal body parts, remaining blood mixes with less-oxygenated blood from the right ventricle, which has bypassed the pulmonary circulation through a third shunt, the ductus arteriosus, facilitated by a high pulmonary vascular resistance.[2,5] A substantial fraction of the mixed blood

returns to the placenta via the umbilical arteries, while the remainder supplies the lower fetal body parts and abdominal viscera.[5,6]

Fetal neurodevelopment

Brain development begins during week four of gestation with the formation of a forebrain (primary prosencephalon), midbrain (mesencephalon), and hindbrain (rhombencephalon) from the neural tube.[7] The forebrain separates into the diencephalon and the secondary prosencephalon.[8] While the former will give rise to the thalamus and epithalamus, the latter will develop into hypothalamus, retina, and telencephalon comprising cerebral cortex, hippocampus, and basal ganglia.[8,9] The mesencephalon does not further subdivide but comprises the most cranial part of the brainstem.[8] The medulla and pons of the brainstem and the cerebellum will develop from the hindbrain, from which also the spinal cord will extend.[8]

Brain development is initiated by rapid proliferation of neuronal precursor cells within the (periventricular) germinal matrix, which begin to differentiate at eight weeks gestation and subsequently migrate to their destined location.[7] This results in growth and increased folding of the cortex.[10] Following migration, which is completed at approximately 29 weeks gestation, the neurons start to synapse.[7] A prominent role in this process plays brain-derived neurotrophic factor (BDNF), expression of which is dependent on neuronal activity.[11,12] Established neural circuits are quickly stabilized by myelination of neuronal axons visible as white matter.[7] Synaptogenesis and myelination continue long into adolescence and interruption can cause severe neurodevelopmental impairment.[7]

Vascularization of the brain

The brain derives its blood supply via the internal carotid and subclavian arteries, which gain their familiar morphology by seven weeks gestational age.[2] The first

branches into the anterior, middle, and posterior cerebral arteries (ACA, MCA, and PCA, respectively), which supply the cerebral hemispheres.[13] The latter gives rise to the vertebral arteries, which join to become the basilar artery, supplying brainstem and cerebellum.[13] A connection between the PCA and basilar artery develops, forming an anastomosis between the two vascular systems (the 'Circle of Willis'), while the carotid origin of the PCA regresses.[14,15] Vascularization of the retina occurs only by the final trimester after maturation of the lens and regression of the hyaloid artery from lens to retina. [9,16] This artery is later known as the central artery of the retina and constitutes a branch of the ophthalmic artery, which originates from the internal carotid.[9]

Intracerebral microvascularization develops early from the perineural (extracerebral) vascular plexus, from where capillaries penetrate deep into the brain tissue by angiogenic mechanisms, establishing an anastomotic plexus at the subventricular zone.[17-19] From here, the brain parenchyma is vascularized in an ascending fashion, continuously reshaping according to neurodevelopmental needs, not to be complete within cortical areas until the age of 4 years.[17,20,21] This angiogenic process is driven by vascular endothelial growth factor (VEGF), which also promotes survival of neurons and glial cells and axonal outgrowth.[22] Interaction between the vascular endothelium and parenchymal astrocytes results in the formation of a blood-brain barrier (BBB), which limits the cerebral permeability to circulating cells or particles and safeguards cerebral extracellular homeostasis.[23] Maturation of the BBB is not complete until a few weeks after term.[21,24]

An important feature of the brain is cerebrovascular autoregulation. It is the ability of the brain to preserve adequate cerebral perfusion despite fluctuations in blood pressure and oxygenation.[25] Functionality of adaptive vasodilation and constriction depends on the maturation of neurovascular mechanisms, which

starts at 23 weeks gestational age and is not yet fully established at term.[19,21] Impairment of the cerebral autoregulation may cause cerebral ischemia and hemorrhage.[26]

Fetal growth restriction

Fetal growth restriction (FGR) is a condition defined as fetal growth below its constitutional growth potential and is therefore not to be used interchangeably with being small-for-gestational age, which also includes fetuses or neonates being constitutionally small.[27] FGR may be caused by chromosomal or genetic syndromes, multiple gestation, congenital infection or metabolic disease, drug use, or inadequate maternal nutrition, but most common is placental insufficiency associated with gestational hypertension, preeclampsia (PE), diabetes, smoking, or other forms of abnormal uteroplacental development.[28,29] Moreover, there seems to be a difference in placental pathology relative to onset of fetal growth restriction, with the placentas of early-onset fetal growth restriction (before approximately 32 weeks gestational age at diagnosis) showing more histologic signs of maternal vascular (uteroplacental) underperfusion, while late-onset fetal growth restriction is more associated with fetoplacental (villous) lesions.[30,31]

Placental insufficiency and fetal hemodynamic redistribution

The placenta is the organ that supplies the fetus with oxygen and nutrients and removes waste back to the maternal circulation.[32] Development of the placenta starts with the invasion of trophoblasts, the outer cell layer of the embryonic blastocyst, into the maternal endometrium and its capillary network.[33] This results in the formation of large sinuses, the so-called intervillous space, where exchange of gas and metabolites takes place.[33] The spiral arteries, which originate from the uterine arteries and supply the endometrium, are being remodeled and lose their smooth muscle layer, which turns them into highly dilated vessels with low

vascular resistance.[34] Fetal trophoblasts further bulge into the intervillous space to form the chorionic ('anchoring') villi, which develop an extensive network of capillaries connecting to the fetal umbilical veins.[35]

Impaired remodeling of the spiral arteries is seen in early-onset PE.[36] Failure of dilation causes high jet velocities and high perfusion pressure in the intervillous space, which is damaging to chorionic villi and decreases the fetal capillary network.[34,37] High uteroplacental resistance subsequently results in reduced placental perfusion and fetal hypoxia on the one hand and maternal hypertension and organ damage on the other.[34,36] Although the pathophysiology of PE is much more complex and not yet fully understood, impaired placental perfusion can be detected during prenatal Doppler ultrasound as an increased resistance in the umbilical artery (UA), which normally decreases with progression of pregnancy.[38] As a compensatory response to hypoxia, the fetus redistributes its cardiac output with preferential perfusion of the brain at the expense of the systemic perfusion.[39] Whether this is neuroprotective and an active fetal mechanism is still controversial.[40,41] However, this so-called 'brain-sparing' effect becomes apparent on prenatal Doppler as a decrease in resistance of the fetal MCA following cerebral vasodilation.[42] Moreover, with progressive hypoxia, intracerebral regional redistribution seems to occur from higher towards lower order brain functions as the fetus starts to decompensate.[43-45] Postnatally, body size of FGR infants with fetal brain-sparing may be asymmetric with a disproportionately large head (although still too small for gestational age) relative to body weight.[40]

There has been much interest in the prevention and therapy of placental insufficiency. Promising options include oral phosphodiesterase 5 (PDE-5) inhibitors and local injections increasing placental VEGF expression.[46,47] However, up to date, no effective and safe treatment of placental insufficiency exists and

FGR remains associated with a high risk of perinatal death and (iatrogenic) preterm birth.[47]

Preterm birth

Preterm birth is defined as birth before 37 weeks gestational age and its complications are the leading cause of global childhood mortality under five years of age.[48] In Europe, about 9% of all live births are preterm and of these, 15% occur before 32 weeks' gestation.[49] Well known causes of preterm birth comprise placental insufficiency and fetal growth restriction, maternal respiratory and urinary infections, abnormal placentation, cervical insufficiency, ascending intrauterine infection, and/or congenital anomalies.[50-52] Further risk factors include multiple pregnancy, maternal stress and nutritional status, substance abuse, and genetic predisposition.[53] However, the majority of preterm births will be classified as idiopathic as no identifiable reason can be found.

Postnatal hemodynamics

With birth, the fetus enters a transitional phase, in which it adapts to postnatal life. It starts with the first breath and inflation of the lungs, which instantly lowers the pulmonary vascular resistance and increases pulmonary perfusion by the right ventricle.[54] Fetal lung fluid is absorbed and enters blood plasma increasing the circulating volume.[54] (Early) clamping of the umbilical cord results in a sudden decrease in preload and increase in afterload to which cardiac contractility and output have to adapt.[55,56] Preload gradually increases with improved ventilation and increased left atrial return from the lungs.[57] Cardiac remodeling towards left ventricular predominance begins.[57] Within hours to days, the ductus arteriosus, foramen ovale, and ductus venosus close.[58,59]

These sudden hemodynamic changes are particularly challenging for preterm and FGR neonates, which usually need ventilatory and sometimes hemodynamic

support. The neonatal lungs may struggle with the clearance of amniotic fluid and inflation due to immaturity of sodium channels, cesarean delivery, and surfactant deficiency.[60] The heart has a reduced ability to increase contractility and output to maintain adequate perfusion. This may be associated with an immature myocardium in the preterm infant or a decreased cardiac reserve following FGR-associated compensatory cardiac adaptation to intrauterine hypoxia.[61-64] Perinatal asphyxia (oxygen deprivation) as it may occur with placental insufficiency, may further depress cardiac function.[64] A depressed cortisol and catecholamine surge due to cesarean delivery and/or immature adrenal glands further contributes to postnatal hypotension and ineffective clearance of lung fluid.[60] Moreover, the ductus arteriosus may fail to close, causing decreased systemic perfusion and pulmonary hypertension as blood is now shunted into the opposite direction, namely from the aortic arch back into the pulmonary vasculature.[5] While any fluctuations in perfusion pressure and oxygenation especially affect organs with less effective autoregulation, such as the intestines or kidneys, cerebral autoregulation should spare the brain.[65] However, cerebral autoregulation in preterm FGR neonates is frequently impaired, which relates to a combination of immaturity, asphyxia-associated vasoparalysis, and overriding brain-sparing mechanisms.[66,67] Sickness and maternal or neonatal medication may further interfere with autoregulation and stable cerebral hemodynamics.[68-71]

Outcomes associated with preterm birth and FGR

Neonatal complications of preterm birth and/or FGR are manifold and largely associated with organ immaturity and underlying pathology.[72] They include respiratory distress, bronchopulmonary dysplasia (BPD), persistent pulmonary hypertension (PPHN), a patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), hypoglycemia, hyperbilirubinemia, anemia, sepsis, peri- and intraventricular hemorrhage (PIVH), periventricular leukomalacia (PVL), and

retinopathy of prematurity (ROP).[73-76] In The Netherlands, the survival rate for neonates born before 24 weeks gestational age is less than 10%, but with active intervention from 24.0 weeks onwards rises to about 60% at 24.0 weeks and almost 100% by 32.0 weeks of gestation.[77] Although advanced perinatal care has led to improved outcomes of preterm infants, survival without major morbidity, in particular of those born extremely preterm, remains a challenge.[78-80] Moreover, there is an increased risk for chronic kidney disease, metabolic syndrome, cardiovascular disease, and neurodevelopmental problems in later life, particularly in those born following FGR.[81-85]

Brain injury and neurodevelopmental abnormalities after preterm birth and FGR

Preterm birth has been associated with altered regional brain volumes. Major risk factors are white matter injury, which presents a loss of myelinating oligodendrocytes associated with hypoxia- or inflammation-induced excitotoxicity, and FGR.[86,87] Structural abnormalities associated with FGR likely reflect regional hemodynamic redistribution and include reduced cortical, hippocampal, and cerebellar volume, altered vascularization, delayed myelination, reduced synapsing in pre-frontal or limbic systems, and impaired neuronal migration.[88] Accordingly, preterm and FGR infants more often struggle with abnormal neurodevelopmental outcomes than term and appropriate-for-gestational age infants. These include cerebral palsy or minor motor impairments, epilepsy, sensory impairments, cognitive deficits, behavioral abnormalities, attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and language difficulties.[89-91] Impairments may become apparent as minor academic difficulties but can also be severely disabling.[92]

Assessment of brain damage is therefore routinely performed in preterm and FGR infants. Serial cranial ultrasound can effectively detect PIVH and PVL (ischemia of the white matter at the watershed zones around the lateral

ventricles), while magnetic resonance imaging is better in detecting cerebellar hemorrhage or mild white matter injury.[93,94] (Amplitude-integrated) electroencephalography can further aid in the prediction of white matter damage-associated neurological outcome and assessment of the variability and complexity of the early motor repertoire (general movements) may predict motor abnormalities and cognitive dysfunction.[95-98]

Hypoxic brain injury

As one may expect, hypoxia plays a pivotal role in brain injury. Hypoxemia disturbs mitochondrial adenosine triphosphate (ATP) generation and consequently ATP-dependent maintenance of an electrochemical gradient across the cell-membrane.[99] In addition to cellular edema, this causes decreased uptake of extracellular glutamate by astrocytes and increased glutamate release by neurons.[99] Excess glutamate in turn overactivates synaptic and extrasynaptic glutamate receptors, which causes excess calcium influx and induces pro-apoptotic pathways.[100] Moreover, excessive calcium within the mitochondria enhances mitochondrial generation of harmful reactive oxygen species (ROS).[101,102] This production of ROS requires oxygen, which explains an additional oxidative tissue injury by ROS upon reperfusion.[101] In addition, microglial overactivation by glutamate causes disruption of the BBB and neuroinflammation.[103] However, a glutamate imbalance seems to be particularly harmful to immature oligodendrocytes, which express higher levels of glutamate receptors than mature oligodendrocyte.[104,105] Prenatal magnesium sulfate ($MgSO_4$) intravenously administered before imminent preterm birth has shown to protect the immature brain from excitotoxic injury by blockade of glutamate receptors, which has shown to effectively decrease the risk of cerebral palsy.[100,106,107] Since moderate hypoxia is necessary for early embryonic and fetal (neuro)development, hypoxia may be especially harmful in advancing gestational

age where metabolic demands increase.[108] However, if oxygen saturations are too low in early gestation this may disturb critical developmental processes, such as neuronal migration and synaptogenesis as outlined earlier.[108]

Hyperoxic brain injury

Hyperoxia has also demonstrated to be harmful to immature brain tissue and has been associated with reduced synaptic plasticity and myelination.[109] While the fetal brain develops well at relatively low arterial oxygen tensions of about 25 mm Hg, slowly increasing until term, oxygen tension quickly rises to about 70 mm Hg following birth.[109,110] A consequential increase in ROS generation from an oxygen-rich environment cannot be effectively counterbalanced until maturation of the antioxidant defense in the third trimester.[109] Thereby hyperoxia is particularly harmful at low gestational age and preterm birth. As ROS react with various kinds of molecules, oxidative stress may damage DNA and mitochondrial membranes and eventually induces apoptosis.[111] Moreover, ROS production seems to be especially high in motor neurons and disturb adjacent astrocytic glutamate reuptake.[112] In addition, ROS cause lipid peroxidation, which disrupts the myelin sheath.[109,113] Damage is potentiated, if hyperoxia is preceded by hypoxia-induced excitotoxic damage, which commonly occurs with placental insufficiency or immaturity-associated hemodynamic fluctuations.[109]

Alterations in gene expression and methylation by hypo- and hyperoxia

In addition to direct cell injury, hypo- and hyperoxia may also interfere with the expression of genes important for normal maturation and neurodevelopment. In the brain, this has become particularly evident for retinal tissue, in which a sudden rise in oxygen tension following preterm birth results in downregulation of VEGF and angiogenesis.[114] Reduced retinal vascularization in turn leads to retinal hypoxia as the retina matures, upon which uncontrolled upregulation of VEGF and

angiogenesis result in the formation of tortuous, leaky vessels, hemorrhage, and in severe cases detachment of the retina and blindness.[114] In the postnatal period, arterial oxygen saturation (SaO_2) is therefore kept within a narrow moderately-high range to reduce hyperoxic exposure and the incidence of ROP without increasing the risk of hypoxia, NEC, and mortality.[115]

The transcription factor hypoxia-inducible factor 1 (HIF1) is a key regulator of the hypoxic response, although other factors such as cAMP response element binding protein (CREB) also appear to be involved.[116] The alpha-subunit of HIF1 stabilizes in response to low oxygen concentrations, dimerizes with its beta-subunit and binds to the hypoxia-response element (HRE) in the promotor region of its target genes.[116] The most popular target genes include *VEGF* and erythropoietin (*EPO*), which stimulate angiogenesis and the production of erythrocytes, respectively, alongside neurotrophic functions.[22,117] In addition, hypoxia is able to induce epigenetic modifications, which act in concert with HIF1, and thereby long-term alterations in genetic expression, which has been implicated as an important component of embryogenesis, neurodevelopment, and disease.[116,118,119] Indeed, several neurodevelopmental disorders, such as schizophrenia and autism, have been linked to hypoxia and the downregulation of VEGF and glutamate receptor units.[120] Moreover, experimental studies have shown that deletion of the HRE region in the VEGF gene causes motor neuron degeneration and that hyperoxia in neonatal mice reduces the expression of BDNF, underlining the regulatory role of oxygen in neurodevelopment.[121,122]

Monitoring tissue oxygenation with near-infrared spectroscopy

Postnatal regional tissue oxygen saturation (rSO_2) can non-invasively be measured in the neonate using near-infrared spectroscopy (NIRS). Several devices exist, but here we will only address the INVOS device as used at our neonatal intensive care unit. Its technology utilizes tissue translucency to near-infrared light at a

wavelength spectrum of 730-810 nm, which is differentially absorbed by oxygenated and de-oxygenated hemoglobin and maximally separated from the absorption spectrum of water, preventing its interference.[123] Melanin, a pigment found in hair and skin, and bilirubin, a breakdown product of heme present in the skin with neonatal icterus, also well absorb light within the same wavelengths, which can lower rSO_2 measurements and produce outliers.[124] However, directional changes in rSO_2 remain visible, allowing for adequate trend monitoring.[125]

Near-infrared light is delivered to the tissue by an emitting diode located within the sensor placed on the skin above the tissue of interest. Unabsorbed light is reflected and detected by two optodes located next to each other on the same sensor, as visualized in Figure 1. The signal returning to the optode situated closer to the light source is subtracted from the signal returning to the optode further away, thereby reducing signals from superficial tissue such as skin and bone.[126]

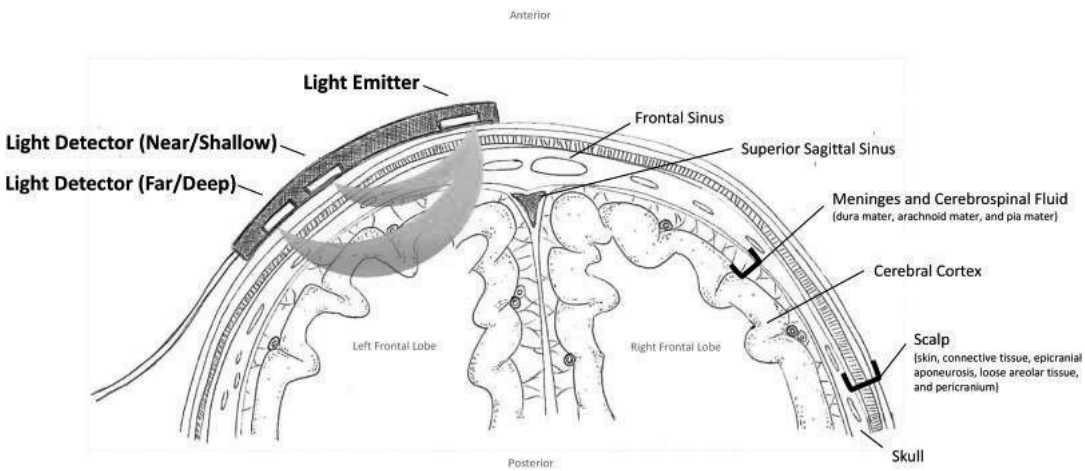

Figure 1. Monitoring (cerebral) tissue oxygenation with near-infrared spectroscopy. Adopted from Zaleski et al.[127]

In contrast to pulse oximetry, which subtracts non-pulsatile flow measurements to be able to measure only arterial oxygen saturation, NIRS measures reflections from the whole tissue microcirculation.[128] As the venous bed is largest, rSO_2 largely reflects venous oxygenation.[129] Simultaneous use of NIRS and pulse oximetry therefore allows calculation of the fractional tissue oxygen extraction (FTOE) using the formula FTOE = $(SaO_2 – rSO_2)/SaO_2$, which is an indicator of tissue ischemia, as it reflects the balance between oxygen delivery and consumption.[130]

NIRS is becoming increasingly popular in neonatal intensive care, although its clinical use and interpretation remains subject of extensive research.[131] Cerebral NIRS has demonstrated to be of particular value in preterm and FGR infants as it visualizes changes in cerebral perfusion associated with cardiorespiratory immaturity and transitional complications.[132] Simultaneous monitoring of the splanchnic and renal tissue can be useful to early detect and interpret changes in global oxygenation status.[133] Figure 2 depicts the typical sites for NIRS monitoring in the neonate. Moreover, multisite NIRS can reflect fetal hemodynamic redistribution and brain-sparing associated with FGR, which may persist for several days after birth.[134]

Cerebral oxygenation in the detection of brain injury

In newborn piglets, a cerebral rSO_2 below 35% has been associated with ischemic tissue damage and abnormal cerebral function, although this value may vary with different types of sensors.[135,136] Likewise, a high cerebral FTOE, reflecting tissue hypoxia either due to increased cerebral perfusion or decreased cerebral metabolism, has been associated with a higher risk of PVL.[137] Its association with PIVH is less straightforward, as the pathophysiology of PIVH involves initial hyperperfusion and subsequent hypoperfusion.[138,139] Assessing the correlation between cerebral rSO_2 and blood pressure can, however, detect impairment of

cerebral autoregulation, predict the risk of PIVH and PVL, and may aid in hemodynamic therapy.[140]

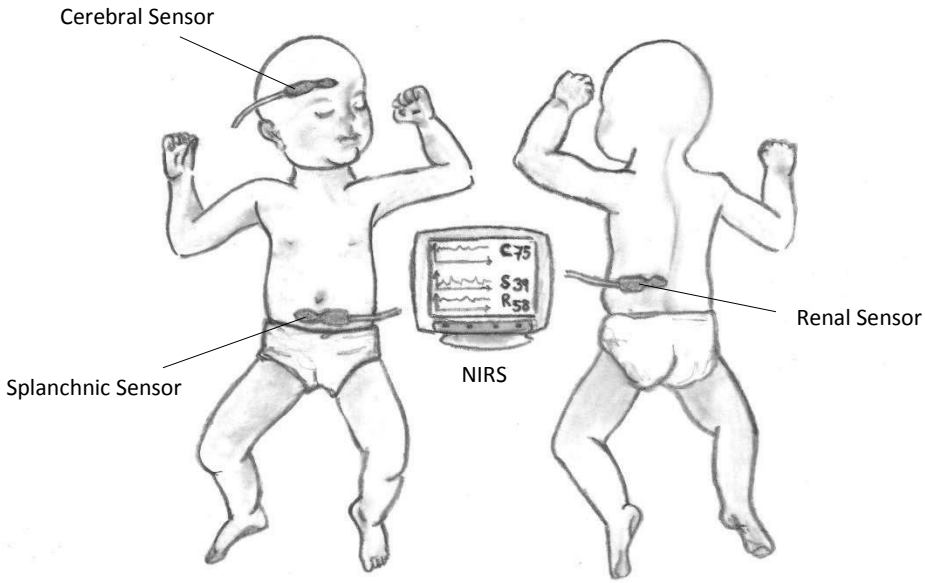

Figure 2. Sensor locations in cerebral, splanchnic, and renal near-infrared spectroscopy (NIRS).

Although gestational age-associated reference values for cerebral rSO_2 and FTOE have been determined for the postnatal period and attempts have already been made to reduce the cerebral hypo- and hyperoxic exposure, optimal saturation ranges in relation to brain development and function remain unknown.[141-144] To effectively interpret and address cerebral oxygenation in preterm and FGR infants and improve neurologic outcome, we first need to better define and comprehend cerebral normoxia and how it relates to perinatal complications and therapies.

Aims and outline of this thesis

Given the high vulnerability of the brain and hemodynamic system in preterm and FGR neonates during the perinatal period, this thesis aims to contribute to an improved understanding of the perinatal cerebral and systemic tissue oxygenation, including fetal brain-sparing, and associated neurodevelopmental outcome in this patient population.

Part I of this thesis deals with the influence of prenatal medication and placental dysfunction on the cerebral and systemic tissue oxygenation of the preterm and/or FGR infant. The following research questions will be answered:

Chapter 1: Do maternal medications with antihypertensive properties, such as labetalol, nifedipine, and $MgSO_4$ affect the cerebral, renal, and splanchnic tissue oxygenation of preterm infants?

Chapter 2: Are changes in postnatal cerebral tissue oxygenation following prenatal $MgSO_4$ exposure related to changes in cerebral metabolism or perfusion and can they be differentiated from underlying hemodynamic effects of PE and fetal brain-sparing?

Chapter 3: Does prenatal sildenafil treatment for severe-early onset FGR affect postnatal cerebral and renal tissue oxygenation?

Part II of this thesis will address neurologic outcomes of fetal brain-sparing and postnatal cerebral tissue oxygen saturation. The following research questions will be answered:

Chapter 4: Is a prolonged duration of cerebral hyperoxia associated with the development of severe retinopathy of prematurity?

Chapter 5: How do fetal brain-sparing and postnatal cerebral oxygenation relate to intelligence, behavior, and executive functioning at 4 years of age in children born following FGR?

Chapter 6: Is fetal brain-sparing in FGR associated with differential oxygen-dependent methylation of neuroprotective genes at 4 years of age?

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PART I

POSTNATAL CEREBRAL AND SYSTEMIC TISSUE OXYGENATION IN RELATION TO PRENATAL MEDICATION AND PLACENTAL DYSFUNCTION